UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/151,612	09/11/98	KOHN	L 5616/3

HM12/0426

ROGERS & WELLS
200 PARK AVENUE
NEW YORK NY 10166-0153

EXAMINER	
CONNELL, Y.	
ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/151,612	Kohn et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-75* is/are pending in the application.

Of the above, claim(s) *36-41, 47-59, 67-73,* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-35, 42-46, 60-66, 74, and 75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

References cited in the IDS have not been considered because they were unavailable at the time of examination.

Applicant's election without traverse of Group 1, claims 1-35, 42-46, 60-66, and 74-75, in Paper No. 8 is acknowledged.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 46 is rejected under 35 U.S.C. 101 since the claimed invention is directed to non-statutory subject matter. The terminology used in claim 46, "mammalian cell derived from a host organism", encompasses cells as implanted in a human or in a human who has been made transgenic by the presence of such constructs, as well as the human thereof. Claims directed to or including within its scope a human, will not be considered patentable subject matter under 35 U.S.C. 101. The grant of a limited, but exclusive property right of a human being is prohibited by the Constitution. See 1077 OG 24.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 40, 46, and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40 and 46 are rejected for use of the language "capable of", which is considered indefinite, since the language "capable of" is considered to be drawn to some conditional function which is a latent characteristic, the scope of which is unclear in the claims.

Claim 46 is also rejected because it is unclear how the antigen presenting cell would have the ability of increasing antigen presentation by a mammalian cell derived from a host organism. Does applicant mean an antigen presenting cell from a mammalian host organism, with the ability of increasing presentation of an antigen to a mammalian cell? Would applicant please clarify?

Claim 74 is rejected because it is unclear what applicant intended. Does the method of increasing presentation of antigen by a cell derived from a host organism, mean that the double-stranded polynucleotide would be introduced into the mammalian cell *in vitro* or *in vivo*?

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-35, 42-46, 60-66, and 74-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the expression of an immune response recognition molecule comprising MHC class 1 and 2, in a mammalian cell such as thyroid FRTL-5 thyrocyte, by introducing a double-stranded polynucleotide such as DNA, into the cell comprising, activating expression of a gene or gene product involved in antigen presentation, growth, and function of the cell, such as CIITA, and increasing the ability of a cell to present antigen to an immune cell, does not reasonably provide enablement for a method of increasing the expression of any immune response molecule of any origin, in any mammalian cell by introducing any double-stranded polynucleotide into the cell comprising, activating expression of any gene or gene products involved in antigen presentation, growth, and function of the cell, and increasing the ability of the cell to present antigen to any immune cell. Neither does the specification provide enablement for a method of treating a mammalian disease sensitive to immunotherapy, such as cancer, nor wherein the mammalian disease is an intracellular infection caused by virus, bacteria, yeast or protozoa, nor wherein the mammalian disease is caused by environmental injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

1. Claimed invention. The claims are drawn to a method of increasing the expression of an immune response recognition molecule in a mammalian cell by introducing a double-stranded polynucleotide into the cell, comprising activating expression of a gene or gene product involved in antigen presentation, growth, and function of the cell, and increasing the ability of the cell to present antigen to an immune cell.

The claims are also drawn to a method of increasing the expression of an immune response molecule wherein the expression of the gene or gene product is activated through a cellular signal, and wherein the cell can induce an autoimmune response when injected into its host organism, and wherein the cell recruits and activates T cells, and produces at least one soluble mediator of immunity.

The claims are further drawn to a method of increasing the expression of an immune response molecule in a mammalian cell wherein the double-stranded polynucleotide is additive to and independent of an interferon-mediated increase in the expression of the MHC molecule, wherein the double-stranded polynucleotide is RNA which increases beta-interferon produced by the cell, and increases immunogenicity of the cell in a host organism.

Finally, the claims are drawn to a method of treating mammalian diseases sensitive to immunotherapy, or wherein the disease is an intracellular infection caused by virus, bacteria, yeast or protozoa, or wherein the mammalian disease is caused by environmental injury, as well as a method for increasing presentation of an antigen by a cell derived from a host organism, wherein

the cell is a tumor cell and the immunized host organism has an increased ability to recognize and kill the tumor cell.

2. The *in vitro* and *in vivo* examples and results on pages 46-134, shows that applicant was successful in demonstrating that viral infection of mammalian cells increases MHC gene expression differently from gamma-interferon, and that replacing the virus with any double-stranded polynucleotide such as viral, bacterial or mammalian DNA, produces the same result or effect. The applicant was also successful in demonstrating that the actions of double-stranded nucleic acids to increase gene expression was additive with gamma-interferon, and mimics tissue damage induced by exogenous insults. Applicant was successful in demonstrating the ability of double-stranded polynucleotides to enhance expression of the 90Kd associated immunostimulator implicated in host mechanisms to defend against tumors and AIDS, wherein the double stranded polynucleotide regulates cell cycle progression and growth, differently from gamma-interferon. Finally, the *in vivo* results demonstrate that applicant was successful in inducing in mice, an autoimmune disease which mimics Graves' disease in humans.

3. It is not readily apparent that one skilled in the art given applicant's disclosure alone, would be able to practice the invention over the scope claimed in view of the lack of guidance provided in the specification as filed, and the known unpredictability in the art. In the instant situation, the claims embrace a method of increasing any immune response recognition molecule in any mammalian cell by the introduction of any double-stranded polynucleotide into the cell. The specification gives specifics only for the MHC class I and II recognition molecules, the

FRTL-5 mammalian thyroid cell, and DNA and RNA as double-stranded polynucleotides. It remains unclear that the state of the art at the time of the invention was such that one could routinely increase expression of immune recognition molecules obtained from any species, in any mammalian cell, by the introduction of a double-stranded polynucleotide from any bacteria, protozoa, virus or mammalian cell, as broadly claimed. Such is considered to require undue experimentation.

The specification fails to provide an enabling disclosure for methods of treating mammalian diseases sensitive to immunotherapy such as cancer, or diseases associated with intracellular infection caused by virus, bacteria, yeast or protozoa, or disease caused by environmental injuries, by *ex vivo* gene therapy. The specification fails to disclose any credible disease disorders sensitive to immunotherapy. On page 32 of the specification, applicant asserts that autoimmune diseases wherein the invention is relevant includes but is not limited to the delineated list, and includes other diseases as yet to be described. Therefore, applicant is claiming a method whereby any and all recited diseases and others yet to be described would be treated by *ex vivo* therapy of the present invention. Again, this is considered to require undue experimentation.

Gene therapy as a treatment for disease holds great promise. According to W. French Anderson: "The first approved clinical protocol for somatic gene therapy started trials in September 1990. Since then, in just 7.5 years, more than 300 clinical protocols have been approved worldwide and over 3,000 patients have carried genetically engineered cells in their

body. The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions: the efficiency of gene transfer and expression in human patients is, however, disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease.

The specification fails to provide an enabling disclosure for the method of treating a mammalian disease sensitive to immunotherapy, such as cancer, by removing diseased cells from a mammal, introducing a double-stranded polynucleotide into the cells, killing the cells, and immunizing the mammal with an effective amount of the cells to prevent or alleviate the symptoms of the disease. The specification fails to teach how one would identify *in vivo* in a mammal, whether or not the disease is cancer, or the disease is an intracellular infection caused by virus, bacteria, yeast or protozoa, or whether the disease is caused by environmental injury. No teachings are present to guide the skilled artisan in terms of how many cells would be selected and targeted for removal, and how they would be removed for *ex vivo* therapy.

Similarly, the specification fails to provide an enabling disclosure for a double stranded polynucleotide to be introduced into the diseased cells. On page 36 of the specification, applicant states that a polynucleotide is a polymer of ribonucleoside, deoxyribonucleosides, pyrimidine, and purine derivatives, derivatives with a modified base, pentose sugar, and combinations thereof, but fails to state conclusively which double-stranded polynucleotide would be utilized to treat which

specific mammalian disease. Likewise, no teachings are present in terms of how the extracted cells or transfectants would be killed, and how much of the transfectants, at what dosage, in what pharmaceutically acceptable carrier, which when administered to a mammalian subject, would be therapeutically effective in preventing or alleviating symptoms of the disease. The specification fails to teach whether or not the immunization of transfected cells would be a one time dosing, or whether repeat doses would be necessary to prevent or alleviate symptoms of which specific mammalian disease.

The specification fails to provide an enabling disclosure for the method of treatment involving an adjuvant. On page 31 of the specification, applicant states that the present invention may be used additively or synergistically with synthetic ODN expressing stimulatory CpG motifs as adjuvants to boost the immune response to DNA and protein based immunogens when co-administered with protein or DNA-based vaccines, but fails to identify what would be an appropriate adjuvant, or whether or not conventional chemotherapeutic agents or treatment regimens, which when combined with the present invention, would be therapeutically effective in preventing or alleviating symptoms associated with a particular cancer, or other recited mammalian diseases. Neither are teachings present to guide the skilled artisan to assess *in vivo* whether or not the immunization coupled with the adjuvant would be therapeutically effective in ameriolating the diseased state. According to Anderson: "Long term stable expression at an appropriate level must be considered. If the gene stays active within the cell, the cell often dies. The immune system is designed to recognize and eliminate foreign gene products and cells that

produce a foreign protein. Hence the immune system is still likely to recognize a new or modified protein produced by the therapeutic gene; a newly synthesized normal protein would appear abnormal to an immune system that has never been exposed to it (Anderson, see page 26, right col, 1st para)".

4. The physiological art of preventing or alleviating disease symptoms associated with diseases such as cancer, intracellular infection and diseases caused by environmental injuries, by the *ex vivo* method of the present invention, at the time of filing would have been considered unpredictable. At the time of filing, there was no confirmed success in any human gene therapy trial, including trials involving the method of preventing or alleviating disease disorders in a mammalian subject, *in vivo* or *ex vivo*, by administering a double-stranded polynucleotide to extracted mammalian cells, before immunizing the mammalian subject with an effective amount of the transfected, killed cells. W. French Anderson (Nature 392 S, 25-30, 1998) teaches that: "the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding . . . . what regulatory sequences are appropriate for which cell types, and how *in vivo* immune defenses should be overcome". At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

5. In the absence of specific guidance which is lacking in the specification as filed, and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require

undue experimentation for one skilled in the art to practice the claimed methods or use the claimed products as disclosed in the specification.

The quantity of experimentation required to practice the invention as claimed would require the isolation of immune recognition molecules from any species, whether or not they have been characterized and their functions known. One skilled in the art would also determine which double stranded polynucleotide from which organism, when introduced into which specific mammalian cell *in vivo*, would result in an increase in MHC class I and II gene expression. Similarly, it would require undue experimentation to determine for example, which double-stranded polynucleotide when introduced into which specific mammalian cells *ex vivo*, when used as an immunogen would prevent or alleviate symptoms of a specific disease. This presents innumerable variants such that one is left to trial and error experimentation to obtain the intended function. This is considered undue experimentation.

It would also require undue experimentation to determine, in the absence of a specific disease model, what is a therapeutically effective dose of transfected cells to be administered to a mammalian organism, to prevent or alleviate a specific disease disorder. It would also require undue experimentation to determine as well, which specific adjuvant, which when combined with which double stranded polynucleotide, utilized in the treatment of a specific disease, would act synergistically or additively, to prevent or alleviate disease symptoms in a mammalian organism. Such an invitation to experimentation is considered undue.

Claims 1-35, and 42-46, are free of the prior art. At the time of filing, the prior art did not teach or suggest the method of increasing the expression of an immune response recognition molecule in a mammalian cell by introducing a double-stranded polynucleotide into the cell, as claimed. The closest related prior art, Montani et al, 1998 and Saji et al, 1992, both teach the method of increasing the expression of an immune response recognition molecule in a mammalian cell by introducing gamma-interferon into cells.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

April 24, 2000

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600